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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,054	11/17/2000	Gerald R. Crabtree	STAN-166	7611

24353 7590 03/10/2004

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	21

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/716,054	CRABTREE ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

--Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *17 December 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a),. or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: _____.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

ADVISORY ACTION

Interview Summary

1. An interview was conducted on 11/15/03 between Examiner Cook and Attorney Bret Field (37,620). Applicant's draft response to the Final Office Action mailed 17 June 2003 (Paper #23) was discussed. The rejections of record appeared to be overcome, however after careful consideration of the Official Request for Reconsideration (Paper #25 filed 10/17/04) the following rejections were maintained. Rejections not reiterated below have been withdrawn. Currently claims 16-24 are under consideration.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B. Claim 16 remains vague and indefinite because it is unclear as to how binding inhibition will occur. Although the claim recites an interaction between a first target protein and a second binding protein in a host, the method does not clearly outline how the second protein and blocking protein interact such that inhibition of the first and second is accomplished. The claims merely read on the formation of a tripartic complex comprising the bifunctional inhibitor molecule, the target protein, and the blocking protein.

But does not identify the correlation/interaction/detection allowing for comparative analysis between this tripartic complex and the second binding proteins inhibition. Will the blocking protein and second binding protein compete for the same binding site on the target protein therein allowing for measurement of the blocking protein as an inverse measure for the second binding protein? The method does not including essential method steps.

Applicant argues that the claims are not indefinite in light of the specification. The specification clarifies that the tripartite complex prevents access of the second protein to its binding site on the target protein. This argument was carefully considered but not found persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F2d 1181, 26 USPQ 1057 (Fed. Cir. 1993).

Response to Argument

Applicant contends that the claims are not indefinite as to how the 1st first protein and 2nd second protein binding will be inhibited. Further arguing the appropriate method steps have been outlined in the instant claims. This argument was carefully considered, but not found persuasive because the claims remain unclear as to how the bifunctional molecule administered to a host will inhibit 1st and 2nd protein binding. For example will the bifunctional molecule be able to inhibit binding between the two proteins (1st and 2nd) if a complex is already formed in the host prior to administration. Also, once administered is their enhanced specificity of the bifunctional molecule to the 1st protein over the 1st proteins attraction to the 2nd protein or will the bifunctional molecule inhibit only 1st protein molecules that are available for binding.

If the bifunctional molecule only binds available 1st protein it is not clear as to how the method will be operable if the 1st protein is not capable of binding to the administered bifunctional molecule. If the 1st protein is already bound to the 2nd protein or competitively competes with the bifunctional molecule for binding how will the bifunctional molecule inhibit 1st and 2nd protein complex formation? In other words it is not clear how the bifunctional molecule inhibits the 2nd proteins binding to the 1st protein. Accordingly, the claims remain indefinite and rejected under 112, 2nd paragraph.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

II. Claims 16-21 and 24 are rejected under #35 U.S.C. 102(b) as being anticipated by Varshavsky (Proc. Natl. Acad. Sci. USA Vol.95, pp. 2094-2099, March 1998).

Varshavsky teaches multitarget compounds specific for negative targets concerning the concept of co dominant interference. The reference discloses compositions linking two small moiety ligands (< 1Kd page 2095) bipartite compounds consisting of two ligands bound together by a linker (1* and c in Fig. C and D). The ligands are capable of simultaneously binding target protein (C in figure D) and blocking proteins (1 in figure C) thereby possibly forming a tripartite complex.

Multitarget drugs designed according to the specific configurations taught by Varshavsky were taught to be useful in the selective killing of cancer cells via the inhibition of a neurotransmitter-inactivating enzyme in a specific subset of the enzyme-containing cells. Therein teaching protein-protein inhibition. See abstract.

Response to Argument

In response to the argument that Varshavsky et al. do not teach a bifunctional molecule capable of binding two target antigens simultaneously, it is noted that Varshavsky et al. teach both bifunctional molecules (figure 3) and trifunctional molecules (figures 1, 2, and 4). Varshavsky et al. also disclose that these multifunctional binding molecules can be bound to their target antigens via mutually exclusive or mutually nonexclusive means (see page 2096, figure 1, line 14). Therein the reference teaches instances wherein multiple target antigens could be present/bound to the trifunctional or bifunctional molecule simultaneously.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-covalent specific binding) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further the linking group as defined on page 11 of the disclosure is optional.

With regard to teaching away, Applicant argues that the simultaneously bound target protein and blocking protein would not work in the methods of Varshavsky. This argument was carefully considered but not found persuasive because Varshavsky teaches that the mutually exclusive binding of the target proteins to the multifunctional molecules was not essential. For example see page 2096, figure 1 line 13-14. Therefore it appears that the simultaneous binding of target proteins was contemplated byVarshavsky et al. and does not teach away from the instant invention.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Varshavsky (Proc. Natl. Acad. Sci. USA Vol.95, pp. 2094-2099, March 1998) in view of Pouletty et al. (WO 95/10302).

Please see previous discussions of Varshavsky as set forth above.

Varshavsky differ from the instant invention in failing to teach tripartite complexes produced extracellularly.

However, Pouletty et al. teach bifunctional reagents useful in extending in vivo lifetimes of physiologically active agents further reducing the biologically effective concentration or activity of an endogenous or exogenous blood component. Page 2, lines 14-20. A target-binding member, who is a physiologically active agent in a mammalian host is bound to a protein via a reagent or conjugate possibly including a linking group. See pages 19 and 20. Applicable proteins include albumin, transferrin, ferritin, and immunoglobulins. See page 3, lines 5-25. The second binding member is usually a macromolecule of at least 5000 Dalton. Page 25, lines 20-25. The bifunctional reagents are taught to have utility in therapeutic methods to detect host derived and foreign targets. Page 5, lines 6-10.

Varshavsky and Poulett et al. are analogous art because they are from the same field of endeavor, both inventions teach techniques involving bifunctional reagents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the proteins endogenous to the host (i.e. albumin, vitamin receptor, etc..) as taught by Poulett et al. in the method of Varshavsky to perform protein-protein inhibition assay techniques, because such endogenous proteins as taught by Poulett et al. are well known in the art. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such endogenous proteins, because Poulett et al. taught that the selected blocking protein (long-lived blood component) would affect the manner in which the biological activity of the target is modified and the selection will vary dependent on the nature of the target.

Page 30, lines 23-30. In other words compounds endogenous to the host would cause less side effects and extend dosage levels. Page 1, lines 26-30.

One having ordinary skill in the art would have been motivated to do this because the blocking protein can impart its physiological activities to the target-binding member. In this way cellular targets may be inactivated or eliminated. Page 33, lines 16-22.

Response to Argument

Applicant contends that the Varshavsky teaches away from the claimed because the reference only teaches binary complexes. However Varshavsky teaches complexes binding at least four components (a, b, i, along with A,B, or I). The rejection is maintained.

5. For reasons aforementioned, no claims are allowed.

Remarks

6. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Weidenreich et al. (U.S. Patent#5,457,182) teach binding interactions involving FK-506 and FKBP12.6.

B. Maragarnore et al. (U.S.Patent#5,242,810) disclose bifunctional inhibitors of platelet activation and thrombin.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
Remsen 3C-059
(571) 272-0816
2/13/04

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

2/18/04